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REVIEW

Pharmacoeconomics in COPD and inappropriateness of diagnostics, management and treatment☆

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Summary
Chronic respiratory disorders (CRDs) concern many people and generate important health and social costs. Their global impact (particularly that of COPD) has been the subject of numerous pharmacoeconomic studies published in recent years. These studies confirm the growing impact of COPD in all countries, in terms of the patient and patient's family, and that of society as a whole. The attitude towards COPD management is still largely inadequate, from prevention to diagnosis to drug and non-pharmacologic long-term treatment. The pulmonary specialist, in cooperation with other health professionals, can play a fundamental role in detecting inappropriateness in the clinical course of COPD and provide the basis for a correct assessment of pharmacoeconomic issues.

Given the increasing social impact of COPD, the meeting inspiring this review, "COPD a social disease: inappropriateness and pharmacoeconomics. The role of the specialist: present and future", Venice, Italy, 21–22 April 2010, fits in perfectly with the goals and recommendations of GARD (Global Alliance against chronic Respiratory Diseases) of the WHO. GARD has formulated working recommendations: i) to develop national programs of prevention and control of CRDs, starting from health education campaigns and better knowledge of epidemiology, impact, and relative risk factors; ii) to provide training and continuing education on prevention and treatment of CRDs, disseminating the existing guidelines; and

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iii) to facilitate access to essential treatments and favour adherence to long-term treatment, including drug treatment and pulmonary rehabilitation, particularly amongst disadvantaged sectors of the population.

Contents

Respiratory diseases constitute a serious health problem, representing altogether (including lung cancer) the 2nd major cause of mortality worldwide: given the present degree of underdiagnosis they are probably even more frequent than currently anticipated.[1,2] The future trend seems for a further increase, though differentiated for the individual disorders chronic obstructive pulmonary disease (COPD) in particular is one of the major health problems worldwide, negatively affecting patients and their families, the employment sector, and society. Its epidemiological, clinical, social and socio-economic impact is on the rise and there is no evidence of any change in these trends.[3] In fact, COPD is estimated to become the 3rd cause of death worldwide by 2020. These figures make it important to identify risk factors associated with COPD and seek early treatments as soon as lung function impairment and symptoms emerge. At present, most people are not diagnosed until they are in their late 50's when their respiratory lung function has already started to decline in a clinically significant way.[4]

The high level of underdiagnosis/undertreatment or misdiagnosis/mistreatment in the early stages of the disease underscores the problem of inadequate standards of care, that are a general problem even in developed countries, at all levels of intervention from limited prevention through inappropriate long-term management.[5,6]

Prevention

Lifestyle modifications can help prevent COPD, or improve lung function: smoking cessation, avoidance of respiratory irritants, prevention of infections, maintaining balanced nutrition and hydration, avoiding extreme environmental conditions, maintaining proper weight, and exercising to increase muscle tone.[7] However, data are insufficiently evidence-based for some of these factors. Quite solid data exist for active and secondhand tobacco smoke, occupational exposure to respiratory irritants and outdoor and indoor air pollution.[8]

Smoking is the leading cause of COPD worldwide: 80—90% of subjects diagnosed as COPD are long-term smokers according to the American Lung Association. The cumulative "dose" an individual smokes (unit amount per time of smoking) can increase the probability of developing the disease and intensify its severity. Quitting smoking can prevent further lung damage. Besides direct smoking, secondhand smoke exposure and occupational exposures may also influence the development and the progression of the disease and its health outcomes.[8,9] Actually, it has been suggested that an estimated 25—45% of patients with COPD do not report a smoking history, suggesting a burden of non smoking COPD which may be higher than previously believed.[10] About 3 billion people, half the world's population, are exposed to smoke from biomass fuel compared with 1.01 billion who smoke tobacco, which suggests that exposure to biomass smoke might be the biggest risk factor for COPD globally.[10] Byproducts of oxidative stress found in air pollutants (ozone, sulfur oxides, carbon monoxide, nitrogen oxides, and particulate matter) are common initiators or promoters of the damage produced in airways chronic diseases.

Since secondhand smoke is a modifiable risk factor, clinicians, public health experts and politicians should

assess such exposure and counsel its avoidance. In public health terms, the effects of secondhand smoke exposure on susceptible subpopulations should provide a further rationale for laws prohibiting smoking in public.

In 2003 a systematic epidemiological review into occupational factors associated with COPD by the American Thoracic Society showed that about 15% of COPD cases might be attributable to exposure to toxic gases in the workplace, grain dust in farms, and dust and fumes in factories.[9] Use of appropriate protective devices (e.g. face mask) in the workplace to avoid inhaling toxic or irritant substances has been documented as potentially effective.

Exposure to indoor and outdoor air pollutants is a major factor contributing to augment morbidity, healthcare resources utilization and higher mortality among patients with COPD, and largely impacting on public health, but there are few studies on whether air pollution is a key factor in the development of this disease.[10]

Strong evidence exists also for infections as a trigger of COPD exacerbations. Prevention of respiratory infections, such as influenza and pneumonia, can reduce the risk of COPD worsening. Vaccinations can prevent some of the infections that cause COPD exacerbations and should be administered to all patients with COPD, although clinical trial data are limited.[11] Patient and physician barriers to vaccination have to be overcome with targeted education and system-wide interventions. In a large cohort of COPD patients admitted to Italian hospitals for an exacerbation, the percentage of subjects having received vaccination was only 58% and 13% for influenza and pneumococcal vaccines, respectively.[6] More data on risk factors for COPD development, progression and exacerbation, as well as on the role and economic impact of commonly occurring comorbidities (such as asthma), are in any case needed to implement cost-effective prevention and management strategies.

Diagnosis

The diagnosis of COPD has been conventionally based on spirometry and symptoms, in the presence of risk factors such as smoking or occupational exposure.[7] Adding medical history data to spirometry is important as there is still much underpresentation and underdiagnosis of COPD. Thus, diagnostic guidelines should stress the importance of persistent cough and phlegm to support timely diagnosis of COPD in family practice.[12]

The GOLD Committee suggested the use of a fixed FEV_1/FVC cut-off of 0.70 instead of the more appropriate statistically defined lower limit of normal. However, according to a number of recent papers, the fixed cut-off of 0.70 significantly overestimates airflow obstruction in older people leading to misuse of resources, and individual and societal harm.[13–15] On the other hand, it underestimates airflow obstruction in young adults leading to a missed opportunity for early diagnosis of COPD in patients who might benefit from early intervention.[13] Since diagnostic confusion between COPD and asthma is common, bronchodilatation performed after spirometry can reduce the likelihood of misclassifications in the presence of not-fully-reversible airflow limitation.[7]

The complexity and heterogeneity of the disorders encompassed by the term COPD with the overlap of different phenotypes have recently led to the following recommendations: i) to develop a new taxonomy to better define the disorders of airways obstruction and, consequently, ii) to have a more multidimensional clinical assessment.[16] Besides FEV_1/FVC, lung volumes should always be included in the diagnosis of COPD as evaluation of hyperinflation can be an important criterion to phenotype COPD.

Treatment

Over the last two decades the previously nihilistic attitude that smoking cessation was the only possible treatment for COPD has changed to a more active approach. This is the result of several large trials that investigated not only pharmacological agents but also pulmonary rehabilitation and lung volume reduction surgery. The current paradigm holds that COPD is preventable and treatable.[11,17] Despite the valuable evidence-based data gained from these trials, we have to bear in mind a limit: that the study populations were highly selective, i.e. patients were only included if they had COPD without concomitant morbidities which could impact negatively on the trial outcomes. In real life, however, COPD patients often have multiple, symptomatic comorbidities, such as heart disease, osteoporosis, peripheral muscle weakness and dysfunction, anemia, depression, anxiety and lung cancer.[18] Despite this, patients receive treatment based on the trial results whether they meet the basic inclusion/exclusion criteria or not. As a consequence, the implementation of therapies on a large scale requires a close monitoring of treatments as to their safety and efficacy, thereby avoiding undue side effects and negative consequences.

The pathophysiological hallmark of COPD is variable airflow obstruction resulting in pulmonary hyperinflation. The progressive decline in lung function leads to significant limitations in daily life for patients with COPD over time, which include dyspnea, exercise capacity, frequent exacerbations and hospitalizations.

Over the last several years, pharmacotherapy studies have demonstrated that bronchodilators reduce dynamic hyperinflation, increase inspiratory capacity (by reducing the functional residual capacity), decrease work of breathing, and improve ventilatory capacity during activity and formal exercise testing. At a clinical level, bronchodilators improve dyspnea, decrease exacerbations, ameliorate health-related quality of life (HRQoL) impairment, and could possibly decrease mortality.[7,17]

Clinical studies with long-acting bronchodilators, long-acting β2-agonists (LABA, such as formoterol, salmeterol and more recently indacaterol) and long-acting anti-muscarinic agents (tiotropium) have shown significant improvements in trough peak FEV_1 (range, 0.1—0.3 L) and average FEV_1 (range, 0.1—0.25 L) compared to a decline in placebo-treated patients (short-acting β -agonists and/or ipratropium). Comparable results were demonstrated with FVC measurements.[19,20] Clinical studies have evaluated the use of a combination of tiotropium and long-acting β2-agonists showing that there is a synergistic effect of the combination therapy and further improvement in lung function. This combination therapy will be suitable for patients with severe disease.[21]

The sustained improvement in lung function seen in these studies suggests that long-acting bronchodilators may slow the decrease in lung function over time and subsequently change the clinical course of the disease.

Clinical studies using triple therapy — tiotropium and fixed combination of long-acting β2 agonists and inhaled corticosteroid — have demonstrated an enhanced improvement in lung function, and a reduction of exacerbations as compared with individual agents alone particularly in patients with severe and very severe COPD.[22]

An unresolved question, namely whether regular treatment with long-acting bronchodilators and/or the combination of LABA-inhaled corticosteroids should be initiated at an earlier stage of the disease, remains to be answered. Analyses of retrospectively identified subgroups from TORCH and UPLIFT studies show that patients with moderate disease might also benefit from these therapies, with some evidence that there is a reduction in disease progression. These studies showed significant increases in some secondary endpoints which included trough FEV_1, peak FEV_1, dyspnea score, and HRQoL. Notably, patients also have a significant reduction in exacerbations.[20]

Recently there has been concern that the long-term use of inhaled bronchodilators commonly used in the treatment of COPD, including long-acting β2-agonists and anticholinergic drugs, may increase the risk of cardiovascular complications. However, prospective data about the relative risk of therapy in patients with sufficient symptoms to be eligible for treatment is still lacking. The recent analysis of the tiotropium database and the findings of the UPLIFT study in fact indicated a reduced mortality from cardiovascular events. The mechanism by which tiotropium may reduce these events and possibly improves survival could be associated with the reductions in exacerbations and hospitalizations observed. However, conclusive evidence is still lacking. In the pooled analysis of 30 trials, tiotropium treatment resulted in a reduction of serious cardiac adverse events.[23]

β2-agonists have the potential to precipitate cardiac arrhythmias and other cardiac events; however, this has not been regarded as important in clinical practice until recently. In the TORCH study, patients randomised to LABA alone had the lowest rate of cardiovascular death vs. those who received placebo who had the highest rate. None of the predicted risk factors for cardiovascular events (older age, history of previous cardiac disease, worse lung function) interacted with treatment.[24] However, this may not reflect the real world situation since patients with relevant cardiac comorbidities were excluded from these studies.

According to recent controlled randomized trials the risk of pneumonia is increased in patients receiving inhaled fluticasone. In the TORCH study, patients receiving at least 1000 mcg/day of fluticasone propionate equivalent compared with non-users of inhaled corticosteroids within the past year, had a rate ratio for pneumonia hospitalization of 2.25 (95% CI 2.07—2.44). The TORCH trial showed no difference in mortality from pneumonia between patients on inhaled corticosteroids and those on placebo.[25]

The latest class of drugs introduced into COPD therapy are selective phosphodiesterase-4 inhibitors. The recently EU-approved, oral, once-daily PDE4 inhibitor, roflumilast, supposedly targets airway inflammation. Participants in two 6- and 12-month studies on roflumilast alone or in combination with salmeterol and/or tiotropium had significant improvements in lung function, quality of life and reduction in exacerbations. Adverse events were mostly mild in nature. The two most frequent in the roflumilast group were diarrhea and weight loss.[26]

Follow up

COPD exacerbations frequently cause follow up or emergency visits and hospitalizations and represent a major financial challenge for most healthcare systems. A COPD exacerbation has been defined as a change in the patient's baseline dyspnea, cough, and sputum beyond day-to-day variations, with an acute onset, which may warrant a change in regular medication.[11]

Despite international guideline recommendations, the management of COPD exacerbations varies widely among the different settings.[6] Follow up modalities after hospitalization to optimize care and reduce the risk of a relapse, the recurrence of which is greatest within the first few weeks of the initial event are even more diverse.[27,28] Several risk factors for a recurrent exacerbation have been identified: number of previous exacerbations, previous hospitalizations, long-term use of oxygen, lung function, absence of a primary caregiver and choice of pharmacological therapy.[6,29] Specific recommendations for the management of patients after an exacerbation are lacking. Further research is needed to determine the most appropriate functional diagnosis and severity stratification (e.g. spirometry is largely underused),[6] the potential benefits of home monitoring and noninvasive ventilation as well as the benefits of long-term oxygen therapy in borderline respiratory failure, self-management programs and early rehabilitation.

Current guidelines recommend a followup 4—6weeks after hospitalization where clinical status, inhaler technique, the need for long-term oxygen therapy and FEV_1 should be assessed. Whether earlier timepoints after discharge reduce exacerbations is unclear. There are few studies comparing the effects of different frequencies of follow up visits on relapse rates after hospitalization due to a COPD exacerbation.

Available data suggest that early rehabilitation should be included in the follow up program as it reduces the hospitalization rates and improves exercise capacity and quality of life.[30] A large multicenter Italian study demonstrated that only 14.5% of COPD patients admitted to hospital for an exacerbation were offered pulmonary rehabilitation[6] suggesting that rehabilitation for COPD patients in different healthcare settings requires improvement.

Long-term oxygen therapy (LTOT)

Oxygen therapy is essential in COPD patients with chronic respiratory failure. Two prospective and randomized clinical trials — NOTT and MRC — published about 30 years ago[31,32] are today's basis for prescribing oxygen therapy. In these studies survival in stable COPD was improved with long-term oxygen therapy (LTOT) for more than 15 h/day. Improvement in survival has been documented only in COPD with severe chronic hypoxemia ($PaO_2 < 55$ mmHg (7.3 kPa) or PaO_2 ranging from 56 to 59 mmHg (7.4—7.8 kPa) in the presence of cor pulmonale, or a haematocrit of >55%).

The LTOT indications (based on NOTT and MRC) were established in a very selected and limited number of patients which might not represent the heterogeneity of the COPD population. These recommendations have been subsequently extended, albeit without solid evidence, to COPD patients with moderate hypoxemia ($55 < PaO_2 < 65$ mmHg), and to patients with a decreased oxygen saturation ($SaO_2 < 90\%$) during exercise or sleep.[7,17,33] Comorbidities are likely to affect both prognosis and health outcomes in COPD patients but clinical guidelines do not provide adequate guidance for patients on LTOT with complex chronic diseases.

Prior to prescribing LTOT the COPD should be in a stable phase. Unfortunately COPD patients frequently receive home oxygen after an exacerbation, despite the absence of data to support its short-term benefits. In fact, in up to 38% of COPD PaO_2 levels improved beyond those qualifying for LTOT, simply by optimizing medical therapy.[34] The reassessment of the LTOT indication after 3 months of clinical stability can significantly reduce the number of patients requiring LTOT after an exacerbation.[7,17] Given the increasing numbers of patients receiving long-term supplemental oxygen, a critical revision of the actual indications for LTOT is needed, particularly for COPD patients with comorbidities, mild-moderate hypoxemia, exercise and sleep desaturation. Also, given the high overall costs, LTOT should be prescribed only for patients in whom there is a reasonable expectation of clinical benefit.

Non-pharmacological therapies

The National Emphysema Trial (NETT) was the first randomized trial in COPD in which a surgical procedure was evaluated using a medical comparator, in this case optimal medical therapy and pulmonary rehabilitation. In the baseline evaluation and follow up of the patients included in NETT, a very low FEV_1 and diffusion capacity for carbon monoxide (DL_{CO}) were associated with a poor outcome.[35] These observations were important for defining the most appropriate candidates for lung volume reduction.

Several trials have emphasized the benefits of pulmonary rehabilitation with very little evidence regarding side effects. The only drawback related to negative outcome is that of patients who do not want to participate in rehabilitation or do not complete the program. The percentage of patients who do not join programs is very high (around 60%) and out of those who join close to 30% fail to complete the program. Very little has been done to better characterize these patients and evaluate the factors that lead to suboptimal compliance and adherence.[36]

Pharmacoeconomic issues

The cost of pharmacological treatment is steadily increasing in all European countries. The main reasons are expensive new hospital treatments with biological drugs and cancer medications, and the progressive aging of the population increasing the number of people with chronic diseases including COPD.

Around the end of the last century a growing interest in pharmacoeconomic issues corresponded to the overall need for "accountability", and the economic evaluation of operative strategies became the crucial point for decision makers in allocating the diminishing healthcare resources. Although pharmacoeconomic data are not easy to compare among the different national health systems, the following examples will show some common points, in particular: the very high absolute and relative burden of COPD (despite substantial underdiagnosis), the progressive increase of costs with disease severity (the largest share of costs being due to exacerbations and hospitalizations), the high proportion of LTOT costs among overall therapy costs, the inadequate coverage for drug expenses.

The situation in North America

Canada

According to the BOLD survey[37] the prevalence of COPD in subjects aged 40 years or older in Canada is 11.1% (Stage I), 7.3% (Stage II) and 0.9% (Stage III–IV) or about 3.3 million, considerably higher than the official estimate of 750,000 based on reported physician diagnosis.[38]

Primary care providers (PCP) and specialists are usually paid on a fee-for-service basis. Consultation by specialists is generally arranged through a PCP, because services for non-referred patients are paid at a lower rate. The Canadian RUSIC study[39] estimated that exacerbations of COPD requiring a medication change plus an outpatient visit (including to an emergency department) had a mean cost of $641 (CAN 2006 $), whereas the mean cost of an exacerbation requiring hospitalization was $9557. In 2003, the Confronting COPD Survey estimated that the annual direct cost of COPD care including laboratory tests and visits to PCPs and specialists, was almost $2000 per patient, with about half of the costs due to hospitalization.[40] The estimated economic burden of COPD through work loss was $1198 per patient, giving an annual societal cost of $3195 per patient. Costs increased in direct proportion to the severity of COPD as measured by FEV_1 or MRC dyspnea score.

There is no universal drug plan in Canada, and provincial formularies act as barriers against the application of current guidelines.

A survey of Canadian PCP practice patterns in COPD (CAGE study) observed that only 34% of practices surveyed provided treatment that matched guidelines.[41] Non-prescription of long-acting bronchodilators for patients with moderate and severe COPD occurred in 27% and 21% of cases, resp., and prescription of two long-acting bronchodilators for advanced COPD occurred only in 49% of subjects.

The Canadian OPTIMAL trial[42] demonstrated that triple therapy with tiotropium + fluticasone + salmeterol was superior to tiotropium + salmeterol, or to tiotropium alone in terms of lung function, frequency of exacerbations requiring hospitalization and quality of life. A cost-effectiveness analysis[43] based on this trial demonstrated that the incremental cost per exacerbation avoided with tiotropium + fluticasone + salmeterol was $6510 (CAN) and the incremental cost per quality adjusted life year (QUALY) gained was $243,180 (CAN). The authors concluded that neither tiotropium + fluticasone + salmeterol nor tiotropium + salmeterol seem economically attractive alternatives compared with monotherapy with tiotropium for

moderate-to-severe COPD, in the context of an acceptable societal cost per QUALY gained and per exacerbation avoided.

Among non-pharmacologic therapies, pulmonary rehabilitation has undergone cost/benefit analysis in the Canadian context.[44] The cost for a 2-month inpatient followed by 4-month outpatient program was estimated at $11,597 (CAN) to achieve clinically significant improvements in dyspnea, emotional function, and mastery, with >90% of costs due to the inpatient phase.[44] A more recent study demonstrated fewer hospitalizations when COPD patients completed a pulmonary rehabilitation program.[45] The value and potential cost-effectiveness of developing smaller outpatient and home-based rehabilitation programs should also be stressed.[46]

The most significant gains in COPD healthcare utilization may be realized through collaborative self-management education.[47] A Canadian randomized controlled trial comparing case manager-driven self-management education vs. usual care demonstrated a 40% reduction in the need for COPD patients to access healthcare resources including hospitalizations, emergency department visits and unscheduled clinic visits.[48] Primary care is increasingly restructured into multidisciplinary teams with financial incentives to provide comprehensive care including certified respiratory educators-facilitated self-management education.[49]

United States

COPD affects 20–24 million U.S. citizens, and is the 4th leading cause of death with more than 125,000 deaths annually. In 2010, the estimated direct healthcare costs of COPD are $29.5 billion.[50] Of these, $13.2 billion are due to hospital care, $5.5 billion to physician costs, $5.8 billion to outpatient prescription drug costs, $1.3 billion to home healthcare costs, and $3.7 billion to nursing home care. LTOT costs Medicare more than $2 billion per year for COPD and the cost is growing by 12–18% per year.[51] In addition, there are $20.4 billion in indirect costs due to lost productivity from death and disability.

The pharmacoeconomic evaluations of COPD have recently been critically reviewed with generally concordant results.[52] Different studies have demonstrated that Ipratropium in early stage COPD and a combination anticholinergic-β-agonist in more advanced COPD are associated with lower overall healthcare costs, largely due to reduced exacerbations requiring hospital care.[53–55] These observational studies were supported by an economic analysis of two clinical trials of ipratropium-albuterol combination compared to ipratropium or albuterol alone.[56] Both of the ipratropium arms of the study indicated lower direct healthcare costs than albuterol alone, mainly due to a lower number of exacerbations and hospitalizations.

Long-acting β-agonists (LABA) or fluticasone as monotherapy can reduce COPD exacerbations which translates into less healthcare costs.[57,58] A clinical trial comparing tiotropium to ipratropium demonstrated a 26% reduction in exacerbations and 46% reduction in hospitalizations with tiotropium. The cost-effectiveness of ICS was greater in the most severely impaired individuals.[59]

Three economic analyses of the TORCH trial have been published. In one study using the United States cost structure, salmeterol was the most cost-effective drug ($20,792/QALY) followed by salmeterol–fluticasone combinations (SFC) ($33,865/QALY). Fluticasone alone was not considered as cost-effective.[60] A similar Markov-chain analysis of the TORCH trial, using different cost assumptions, found that SFC was the most cost-effective ($52,046/QALY), followed by salmeterol monotherapy ($56,519/QALY) and fluticasone monotherapy ($56,519).[61] In a third analysis of TORCH, using a multinational approach to cost structure, SFC was also found to be most cost effective, compared to salmeterol or fluticasone monotherapy. The cost-effectiveness was considerably lower for SFC in the United States ($77,100/QALY) compared to Western Europe ($24,200/QALY).[62]

A retrospective analysis of a Medicare database showed that SFC was associated with slightly higher cost savings than tiotropium ($110/year), and ipratropium-albuterol ($295/year), but fared substantially better than ipratropium alone ($1235/year).[62] There is also an economic within trial analysis of exacerbation pivotal trials that shows that SFC have an economic advantage in addition to clinical efficacy in reducing exacerbations.[63]

The situation in Europe

Spain

In a recent population-based study the prevalence of COPD in adults 40–70 years of age was 10.2%, with only 27% of individuals with COPD having a previous diagnosis.[64]

Top-down studies reported COPD costs (both direct and indirect) to be around €800 million annually in 1994. In a microeconomic study performed in 1510 patients with ambulatory COPD followed over one year (bottom-up), the average annual costs per patient were $ 1876. In the IBERPOC population-based epidemiological study, the prevalence of COPD was estimated to be 9% in the 40–69 year age group, of which only 22% were diagnosed and received treatment. Therefore, a total of 270,000 subjects would be diagnosed and treated for COPD multiplied by the annual average obtaining a total of $ 506.52 million annually in direct healthcare costs generated by COPD.

In a top-down calculation, hospital costs constituted 36.3% of the total, drug costs 42.2% and clinical consultations and diagnostic tests 22.5%. In the study using the bottom-up focus the hospital costs represented 43% of the total, drugs 40% and consultations and complementary tests 17%.

Thus, the distribution of the costs in these two studies are similar and amount to an average of $13.32 annually for each COPD patient.[65–67]

Scandinavia

The cost of COPD in Denmark amounts to 10% of all healthcare costs. The annual costs for drugs in Scandinavia is around €100 per inhabitant. The cost in Denmark rose from about €2 billion in 2004 to €3 billion in 2008.[68] This is mainly covered by the public health system, some private insurances and to a minor degree by patients. There are large differences between regions in the prescribing pattern of drugs with the same effect and side effect profiles but in some cases a 10-fold difference in costs.

Italy

COPD costs were calculated in 2002 from data collected by 28 Lung Units within the framework of the National Health Service (NHS). Mean cost/patient/year ranged from €1500

to 3912 according to severity. Direct costs, hospitalizations and emergency room admissions in particular, represented the main cost driver,[69] with unacceptable levels for underdiagnosis and mistreatment. Another investigation reported the mean societal cost for COPD at €1308/p/y: 75% of the costs were due to hospitalizations.[70] Investigating via a Markov model the effectiveness of different therapeutic interventions in outcome optimization, it was found that both a prompt diagnosis of disease and exacerbations, together with an appropriate long-term therapeutic approach, represent the most effective strategy to substantially reduce the impact of COPD on patient, healthcare system and society.[71]

In 2008, health resources consumption and costs generated by COPD were calculated in a 1-year nation-wide, bottom-up, observational, prospective multicenter study. Outcomes were compared with those of the previous year.[72] The proportion of moderate and severe COPD was 53.7 and 16.8%, respectively. Mean total costs/p/y were €2723.7, ranging from 913 to 5452. At the end of the survey, requirement of health services had dropped significantly compared to baseline: GP visits by 57.4%; Emergency Care use by 12.5%; hospitalizations by 18.4%. The mean total cost per patient dropped by 21.7% ($p < 0.002$), mainly due to a more appropriate interventional and therapeutic strategy. These data show that the mean total costs/p/y of COPD doubled in a 5-year period in Italy: the same trend has been registered in other countries (such as USA) over the same period. Despite this, and despite the fact that individual costs for COPD exceed by 67.7% the mean per capita expenses of the National Health System, only about 20% of patients receive appropriate treatment for COPD. A recent cross-sectional study supports the evidence that moderate COPD also represents a substantial economic burden for healthcare systems.[73]

Role of the pulmonary specialist

Healthcare planning

An appropriate management of CRDs based on solid epidemiological data requires a global approach defining the best care for the patient throughout the course of the disease, in a sustainable way for the community. Numerous initiatives and studies have been launched. One of these is the Global Alliance against chronic Respiratory Diseases (GARD), an ensemble of national and international organizations guided and coordinated by the World Health Organization (WHO). The role of the pulmonary specialist at global and national level has been delineated within GARD's strategies and corresponding actions.[74]

GARD has formulated the following working recommendations:

- To develop national programs of prevention and control of CRDs, with the double aim of defining the most pertinent strategies and healthcare actions and raising political and social awareness about this public health priority. The first step to attain this goal is health education campaigns and data collection on: the frequency of CRDs, their impact, and the relative risk factors;
- To provide training and continuing education on prevention and treatment of CRDs, disseminating and implementing the existing guidelines;
- To facilitate access to essential treatments and support adherence to long-term management, including drug treatment and pulmonary rehabilitation, particularly amongst disadvantaged sectors of the population.
- Implementing healthcare strategies.

Patients affected by CRDs are managed in a discontinuous and non integrated mode with inappropriate care procedures. Prevention, too is neither systematized nor integrated. Inappropriateness costs both the individual and the community. It has been calculated that GBP £1.3 billion are spent each year in the U.K. for Emergency Care admission (3—4 visits per patient) for a series of 18 diseases, COPD being at the top of the list and asthma in third place. Varying percentages of these visits resulted not appropriate at a retrospective analysis.[75]

An optimal management of CRDs should reduce the crowding of Emergency Care facilities, global healthcare costs, and improve patients' quality of life. The long-term goal must be to reduce the incidence of CRDs, while in a shorter perspective the target is to reduce — in an economically sustainable way — the social and economic burden generated by those already affected, through a greater appropriateness.

The specialist has a definite role to play in primary prevention, early diagnosis and rehabilitation, as guide or coordinator or consultant depending on the type of intervention, in close cooperation with primary care, other health professionals, and patient associations.

The interventions to promote are[76]:

1. To prevent CRDs developing through a consistent reduction of the number of smokers in the community and strict control of risk factors;
2. To improve and anticipate diagnosis, in particular for COPD and asthma, through a more widespread use of spirometry and specialist expertise;
3. To help patients self manage their own disease, through health education and pulmonary rehabilitation;
4. To integrate the care of patients affected by CRDs, through linking specialist care to primary care, and extending end of life treatment to non-oncological conditions.

In concrete terms, the specialist will build up a network in which the Operational Unit functions as the junction for the whole track of respiratory care, from primary prevention to palliative care, according to the following scheme of action:

- *In primary prevention*: implement smoking cessation, increase the opportunity for screening for COPD and associated conditions;
- *In secondary prevention*: increase accessibility to lung function assessment, experiment screening models for associated conditions, such as lung cancer;
- *In improvement of patient management*: further reduce hospitalization through integration with services

in the local community, e.g. home hospitalization, monitoring of patients with chronic respiratory failure, health education, telemedicine; test a model of pulmonary rehabilitation provided in the local community; expand and rationalize semi-intensive treatment; promote the extension of palliative care to patients with severe respiratory failure.

There is evidence that information and communication technologies (ICT) can play an enabling role over the whole range of services, from a better lifestyle and self-management of health to improving HRQoL of patients as well as managing chronic disease conditions.[77] Properly designed innovative health services supported by ICT might have a positive impact on chronic disease modulation and prognosis, shifting resources from traditional acute care to integrated domiciliary long-term care, focusing on early diagnosis and prevention of exacerbation, but they need to be tested in clinical practice to verify if the cost/benefit ratio is compatible with the current healthcare systems.

Adoption of ICT in healthcare is currently a major priority in Europe as shown by the major e-health deployment initiatives (e.g. epSOS) launched through the Competitiveness and Information Framework Program.[78]

To conclude, new studies on the pathogenesis, pathophysiology, pharmacology of COPD will give new insight on how to better classify and treat clinically a set of likely different disorders with the same label. At the same time, it is not redundant to remind that the real challenge for a more appropriate approach to COPD in both an individual and a social perspective is an innovative approach in the frame of chronic healthcare, in which a patient-tailored attitude should prevail over an old concept of a rigid health system offering a very limited range of solutions to different problems. Such a change has started, but it is still far from meeting the minimal recommended standards.[79] There is large scope for quality improvement and the scientific societies of pulmonary specialists can play a pivotal role in implementing recommendations and developing research for reliable performance measures that are necessary in the quest for efficacy, efficiency and equity in the management of COPD as of all other chronic disorders.

Conflict of interest statement

The authors have all read and approved the enclosed version of the manuscript, and declare that there are no conflicts of interest related to the subject treated in this paper.

References

1. Horton R. The neglected epidemic of chronic disease. *Lancet* 2005;**366**:1514.
2. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006;**28**:523–32.
3. Mannino D. Chronic obstructive pulmonary disease in 2025: where are we headed? *Eur Respir J* 2005;**26**:189.
4. Annesi-Maesano I. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir Mon* 2006;**38**:41–70.
5. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk D, Balter M, Ford G, Gervais A, Goldstein R, Hodder R, Maltais F, Road JCanadian Thoracic Society. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease. *Can Respir J* 2003;**10**(Suppl. A):11A–65A.
6. Lusuardi M, Blasi F, Terzano C, Cricelli C, Crispino N, Comarella L, De Benedetto F, Sanguinetti CM, Allegra L, Donner CF. Standards of care and clinical predictors in patients hospitalised for a COPD exacerbation – The Italian SOS (Stratification Observational Study). *Monaldi Arch Chest Dis* 2009;**71**(4):153–60.
7. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management and prevention of COPD (update 2009) Medical Communications Resources, Inc, 2009. http://www.goldcopd.org
8. Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. *Respirology* 2006;**11**:523–32.
9. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi GEnvironmental and Occupational Health Assembly, American Thoracic Society. American thoracic society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;**167**:787–97.
10. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009;**29**(374):733–43.
11. Varkey JB, Varkey AB, Varkey B. Prophylactic vaccinations in chronic obstructive pulmonary disease: current status. *Curr Opin Pulm Med* 2009;**15**:90–9.
12. De Marco R, Accordini S, Cerveri I, Corsico A, Antó JM, Künzli N, Janson C, Sunyer J, Jarvis D, Chinn S, Vermeire P, Svanes C, Ackermann-Liebrich U, Gislason T, Heinrich J, Leynaert B, Neukirch F, Schouten JP, Wjst M, Burney P. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med* 2007;**175**:32–9.
13. Cerveri I, Corsico AG, Accordini N, Niniano R, Ansaldo E, Antó JM, Künzli N, Janson C, Sunyer J, Jarvis D, Svanes C, Gislason T, Heinrich J, Schouten JP, Wjst M, Burney P, de Marco R. Underestimation of airflow obstruction among young adults using $FEV_1/FVC < 70\%$ as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax* 2008;**63**:1040–5.
14. Vollmer WM, Gíslason T, Burney P, Enright PL, Gulsvik A, Kocabas A, Buist AS. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;**34**:588–97.
15. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, Jensen RL, Falaschetti E, Schouten JP, Hankinson JL, Stocks J, Quanjer PH. Using the lower limit of normal for the FEV_1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;**63**:1046–51.
16. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, Aldington S, Beasley R. Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J* 2009;**34**:812–8.
17. ATS/ERS Standards for the diagnosis and management of patients with COPD. Available at: http://www.thoracic.org/COPD/. accessed 01.06.2010.
18. Barnes PJ, Celli BR. Systemic manifestations and co-morbidities of COPD. *Eur Respir J* 2009;**33**:1165–85.
19. Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, Kesten S. Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008;**31**:742–50.
20. Miravitlles M, Antonio Anzueto A. Insights into interventions in managing COPD patients: lessons from the TORCH and UPLIFT® studies. *Int J Chron Obstruct Pulmon Dis* 2009;**4**:185–201.
21. Cazzola M, Di Marco F, Santus P, Boveri B, Verga M, Matera MG, Centanni S. The pharmacodynamic effects of single inhaled

doses of formoterol, tiotropium and their combination in patients with COPD. *Pulm Pharmacol Ther* 2004;**17**:35—9.
22. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, Kessler R. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;**180**:741—50.
23. Celli B, Decramer M, Leimer I, Vogel U, Kesten S, Tashkin DP. Cardiovascular safety of tiotropium in patients with COPD. *Chest* 2010;**137**(1):20—30.
24. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RATORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH clinical endpoint committee. *Thorax* 2007;**62**:411—5.
25. Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Willits LR, Yates JC, Vestbo J. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009;**34**:641—7.
26. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, Rabe KFM2-127 and M2-128 study groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: two randomised clinical trials. *Lancet* 2009;**374**:695—703.
27. Osthoff M, Leuppi JD. Management of chronic obstructive pulmonary disease patients after hospitalization for acute exacerbation. *Respiration* 2010;**79**:255—61.
28. Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;**179**:369—74.
29. Niewoehner DE. Relation of chronic obstructive pulmonary disease exacerbations to FEV_1: an intricate tango. *Respiration* 2009;**77**:229—35.
30. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality: a systematic review. *Respir Res* 2005;**6**:54.
31. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980;**93**:391—8.
32. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981;**1**:681—6.
33. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;**59**(Suppl. 1): 1—232.
34. Eaton TE, Grey C, Garret JE. An evaluation of short-term oxygen therapy: the prescription of oxygen to patients with chronic lung disease hypoxic at discharge from hospital. *Respir Med* 2001;**95**:582—7.
35. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DENational Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;**348**:2059—73.
36. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltais F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T. ATS/ERS Pulmonary Rehabilitation Writing Committee. American thoracic Society/European respiratory society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;**173**:1390—413.
37. Buist A, McBurnie M, Vollmer W, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka EBOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**:741—50.
38. *Life and breath: respiratory disease in Canada*. Public Health Agency of Canada, http://www.phac-aspc.ca; 2007.
39. Mittmann N, Kuramoto L, Seung S, Haddon JM, Bradley-Kennedy C, Fitzgerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. *Respir Med* 2008;**102**:413—21.
40. Chapman K, Bourbeau J, Rance L. The burden of COPD in Canada: results from the confronting COPD survey. *Respir Med* 2003;**97**:23—31.
41. Bourbeau J, Sebaldt R, Day A, Bouchard J, Kaplan A, Hernandez P, Rouleau M, Petrie A, Foster G, Thabane L, Haddon J, Scalera A. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the CAGE study. *Can Respir J* 2008;**15**:13—9.
42. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, Bishop G, Anthony J, Cowie R, Field S, Hirsch A, Hernandez P, Rivington R, Road J, Hoffstein V, Hodder R, Marciniuk D, McCormack D, Fox G, Cox G, Prins HB, Ford G, Bleskie D, Doucette S, Mayers I, Chapman K, Zamel N, FitzGerald MCanadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007;**146**: 545—55.
43. Najafzadeh M, Marra CA, Sadatsafavi M, Aaron SD, Sullivan SD, Vandemheen KL, Jones PW, Fitzgerald JM. Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD. *Thorax* 2008;**63**: 962—7.
44. Goldstein RS, Gort EH, Guyatt GH, Feeny D. Economic analysis of respiratory rehabilitation. *Chest* 1997;**112**:370—9.
45. Rea H, McAuley S, Stewart A, Lamont C, Roseman P, Didsbury P. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. *Intern Med J* 2004;**34**:608—14.
46. Chronic Obstructive Pulmonary Disease Axis of Respiratory Health Network, Fonds de recherche en santé du Québec Maltais F, Bourbeau J, Shapiro S, Lacasse Y, Perrault H, Baltzan M, Hernandez P, Rouleau M, Julien M, Parenteau S, Paradis B, Levy RD, Camp P, Lecours R, Audet R, Hutton B, Penrod JR, Picard D, Bernard S. Effects of homebased pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008; **149**:869—78.
47. Clark N, Dodge J, Partridge M, Martinez FJ. Focusing on outcomes: making the most of COPD interventions. *Int J Chron Obstruct Pulmon Dis* 2009;**4**:61—77.
48. Bourbeau J, Collet J, Schwartzman K, Ducruet T, Nault D, Bradley C. Economic benefits of self-management education in COPD. *Chest* 2006;**130**:1704—11.
49. Rosser W, Colwill J, Kasperski J, Wilson L. Patient-centered medical homes in Ontario. *N Engl J Med* 2010;**362**:e7.
50. National Heart, Lung, and Blood Institute. Morbidity and mortality: 2009 chart book on cardiovascular, lung, and blood diseases, http://www.nhlbi.nih.gov/resources/docs/2009_ChartBook.pdf. accessed 18.01.2010.
51. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report. *Am J Respir Crit Care Med* 2006;**174**:373—8.
52. D'Souza AO, Smith MJ, Miller LA, Kavookjian J. An appraisal of pharmacoeconomic evidence of maintenance therapy for COPD. *Chest* 2006;**129**:1693—708.

53. Hilleman DE, Dewan N, Malesker M, Friedman M. Pharmacoeconomic evaluation of COPD. *Chest* 2000;**118**:1278—85.
54. Jubran A, Gross N, Ramsdell J, Simonian R, Schuttenhelm K, Sax M, Kaniecki DJ, Arnold RJ, Sonnenberg FA. Comparative cost-effectiveness analysis of theophylline and ipratropium bromide in chronic obstructive pulmonary disease. A three-center study. *Chest* 1993;**103**:678—84.
55. Sclar DA, Legg RF, Skaer TL, Robison LM, Nemic NL. Ipratropium bromide in the management of chronic obstructive pulmonary disease: effect on health service expenditures. *Clin Ther* 1994; **16**:595—601.
56. Friedman M, Serby CW, Menjoge SS, Wilson JD, Hilleman DE, Witek Jr TJ. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest* 1999;**115**:635—41.
57. Jones PW, Wilson K, Sondhi S. Cost-effectiveness of salmeterol in patients with chronic obstructive pulmonary disease: an economic evaluation. *Respir Med* 2003;**97**:20—6.
58. Ayres JG, Price MJ, Efthimiou J. Cost-effectiveness of fluticasone propionate in the treatment of chronic obstructive pulmonary disease: a double-blind randomized, placebo-controlled trial. *Respir Med* 2003;**97**:212—20.
59. Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity. *Am J Med* 2004;**116**:325—31.
60. Oba Y. Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD. *Am J Manag Care* 2009;**15**:226—32.
61. Briggs A, Glick H, Lozano-Ortega G, Spencer M, Calverley PM, Jones P, Vestbo J. Towards a revolution in COPD health (TORCH) investigators. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. *Eur Respir J* 2010;**35**:532—9.
62. Dalal AA, Petersen H, Simoni-Wastila L, Blanchette CM. Healthcare costs associated with initial maintenance therapy with fluticasone propionate 250 mug/salmeterol 50 mug combination versus anticholinergic bronchodilators in elderly US Medicare-eligible beneficiaries with COPD. *J Med Econ* 2009; **12**:339—47.
63. Dalal AA, Christensen L, Liu F, Riedel AA. Direct costs of chronic obstructive pulmonary disease among managed care patients. *Int J Chron Obstruct Pulmon Dis* 2010;**5**:341—9.
64. Miravitlles M, Soriano JB, García-Río F, Muñoz L, Duran-Taulería E, Sánchez G, Sobradillo V, Ancochea J. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009;**64**:863—8.
65. Miravitlles M, Murio C, Guerrero T, Gisbert Ron behalf of the DAFNE study group. Costs of chronic bronchitis and COPD. A one year follow-up study. *Chest* 2003;**123**:784—91.
66. Masa JF, Sobradillo V, Villasante C, Jiménez-Ruiz CA, Fernández-Fau L, Viejo JL, Miravitlles M. Costs of chronic obstructive pulmonary disease in Spain: estimation from a population-based study. *Arch Bronconeumol* 2004;**40**:72—9.
67. Izquierdo-Alonso JL, de Miguel-Díez J. Economic impact of pulmonary drugs on direct costs of stable chronic obstructive pulmonary disease. *J COPD* 2004;**1**:215—23.
68. Bildea L, Svenninga AR, Dollerup J, Borgeskov HB, Lange P. The cost of treating patients with COPD in Denmark — a population study of COPD patients compared with non-COPD controls. *Respir Med* 2007;**101**:539—46.
69. Dal Negro R, Berto P, Tognella S, Quareni L. Global outcomes in lung disease study Group. Cost-of-illness of lung disease in the TriVeneto region, Italy: the GOLD study. *Monaldi Arch Chest Dis* 2002;**57**:3—9.
70. Dal Negro R, Rossi A, Cerveri I. The burden of COPD in Italy: results from the confronting COPD survey. *Respir Med* 2003;**97** (Suppl. C):S43—50.
71. Dal Negro R. Optimizing economic outcomes in the management of COPD. *Int J Chron Obstruct Pulmon Dis* 2008;**3**:1—10.
72. Dal Negro RW, Tognella S, Tosatto R, Dionisi M, Turco P, Donner CF. Costs of chronic obstructive pulmonary disease (COPD) in Italy: the SIRIO study (social impact of respiratory integrated outcomes). *Respir Med* 2008;**102**:92—101.
73. Dal Negro RW, Bonadiman L, Turati C, Turco P. Clinical and pharmacoeconomic profile of COPD patients with FEV1 50—60% predicted: pilot study on the impact of the extended indication of ICS/LABA. *Ther Adv Respir Dis* 2009;**3**:51—8.
74. www.who.int/respiratory/gard
75. Nardini S. Schiarire l'aria: uno studio nazionale sulla bronco pneumopatia cronica ostruttiva. *Multidiscip Respir Med*(1): 19—22, www.healthcarecommission.gov.uk, 2007;**2**.
76. De Benedetto F, Donner CF, Nardini S, Sanguinetti CM. La Bpco, la medicina respiratoria e i cambiamenti in corso nell'assistenza sanitaria. *Multidisciplinary Respir Med* 2007; **2**(1):13—5.
77. Blumenthal D. Stimulating the adoption of health information technology. *N Engl J Med* 2009;**360**:1477—9.
78. European Commission. Competitiveness and innovation framework programme (CIP). The 2008—2011 European patients smart open services project (epSOS). *ESF Sci Policy Brief*:1—10. European Science Foundation. Advancing Systems Biology for Medical Applications, www.epsos.eu9, 2008;**35**.
79. Mularski RA, Asch SM, Shrank WH, et al. The quality of obstructive lung disease care for adults in the United States as measured by adherence to recommended processes. *Chest* 2006;**130**:1844—50.